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Feasibility of Field Studies of Multipollutant Interactions

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16. ABSTRACT

The author provides an overview of the problems and progress to date in studies of the respiratory health effects of multiple air pollutants. The problem arises because the preference for single (or even multiple) pollutant in lab studies does not replicate the conditions of actual exposure to complex pollutant mixtures for the general population. The limits of interpretation possible in more realistic studies is stressed. The examples of SO_2-particulate matter and lead-nutritional factors are presented as two cases where laboratory-generated data lagged behind epidemiologic studies in their ability to corroborate multiple exposure-disease associations identified in field studies of humans. An extensive review of laboratory and field studies of multipollutant interactions is provided. The paper ends with a call for more field studies with enhanced measurements of exposures, (e.g. O_3, SO_2, NO_2, acidic aerosols, etc.) and outcomes (e.g. FVC, FEV_1, peak flow rates, particle clearance rates, etc.)

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FEASIBILITY OF FIELD STUDIES OF MULTIPOLLUTANT INTERACTIONS

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INTRODUCTION

The title of this presentation addresses two important questions. One is whether there are significant interactions among pollutants which affect human health. The other, assuming that such interactions do occur, asks whether it is possible to demonstrate such interactions in studies of human populations engaged in normal activities. Before addressing these questions, it is important to define "interactions". The following definition is largely based upon the consensus developed by the National Research Council Committee on Methods for the in vivo Toxicity Testing of Complex Mixtures.[1]

Interaction between components can occur in several ways. Chemicals can interact with each other within a mixture to form one or more new compounds. Upon exposure, some components might affect the absorption, distribution, metabolism, or elimination of other components. Such interactions can lead to toxicity greater or less than would be expected on the basis of the toxicities of the individual components.

Several widely used terms have had varied interpretations. Interaction in general refers to toxicity results that deviate from dose-additive behavior expected on the basis of dose-response curves obtained with individual agents. Biologists tend to think of "synergism" as referring to any result that is greater than simple additivity of linear responses. On the other hand, some statisticians would not view such results as synergistic, but as multiplicative if they are equal to the sum of the logarithms of the doses; they would view results that are greater than multiplicative as synergistic. Such classifications are thus model-dependent; the credibility of a dose-response model depends on the extent to which it is based on some understanding of the biologic mechanisms underlying the interaction.

Current models for describing and extrapolating toxicity data were developed largely for single substances, and their application to mixtures can lead to incorrect inferences when mixture components interact. Several of the most commonly used dose-response models suggest that the probability of response or risk associated with exposure to a mixture at a "low" dose (i.e., with a response rate of about 0.1-1%) is equal to the sum of the risks associated with exposure to the mixture components separately. However, these results are not only dose-limited, but also model-dependent, and the credibility of the result is closely linked to the credibility of the model.

Human experience in terms of the effects of ambient exposures to chemicals differs in some fundamental respects to the exposure-response data base from controlled exposures of humans and experimental animals in laboratory settings. The latter involves controlled situations involving selected populations of known and generally uniform characteristics; known exposure intensities and durations to single chemicals of known purity and characteristics; and determinations of effects, burdens, markers, and so on, at specific known times after exposures. By contrast, the data from human experience almost always involves poorly defined exposures to populations heterogenous in age, sex, and underlying health status. Furthermore, data may or may not be available on significant personal factors that can influence the health endpoints of interest (e.g., use of cigarettes, alcohol, drugs; exercise; diet; etc.). Furthermore, ambient exposures are generally complex mixture exposures. There are either coincident exposures to chemicals other than those that are the

focus of the study, or other, noncoincident exposures to cigarette smoke or dietary factors that can affect the response parameters under study. Interpretation of the human experience generally involves attempts to establish exposure-response relations for active agents and, if possible, the influence of the other identifiable factors. It is seldom possible from these data alone to establish definitively whether the effects of other factors are additive, antagonistic or synergistic, or to assess categorically the roles of age, sex, diet, or preexisting state of health on the responses. However, such studies can and often do generate hypotheses concerning these factors that can be best addressed by follow-up studies involving controlled laboratory exposures.

The NRC report also describes human experience with exposure to chemical mixtures and identifies situations in which standard toxicity-testing protocols did not predict adverse health effects in either a qualitatively or quantitatively adequate manner.(1) The NRC case studies do not represent an adequate cross-section of complex mixtures of current interest. They were, necessarily, selected from cases for which an adequate data base existed to establish that significant effect did occur in human populations and in which there were, at least in retrospect, adequate bases for determining causal relationships. Two of these case studies involved pollutants regulated by National Ambient Air Quality Standards (NAAQSs), and it may be useful to consider the lessons drawn from them. The summaries which follow are those of the NRC Committee.(1)

Sulfur Dioxide (SO_2) and Suspended Particulate Matter (PM)

This case study addresses the classic sulfur-oxide/particulate-matter complex that has been clearly associated with excess daily mortality and respiratory tract morbidity. It is only in recent years that animal models for relevant functional and morphometric effects have proved useful in developing an understanding of the human health effects, and these have involved using animals and exposure protocols not used in conventional toxicological testing (e.g., beagle dogs and diluted auto exhaust mixtures, guinea pigs and SO_2-PM mixtures passed through a heated furnace). Other informative studies involved nonconventional functional assays (e.g., particle clearance function in rabbits undergoing brief daily exposures to sulfuric acid (H_2SO_4) aerosols). Collectively, these animal studies and some studies involving short-term exposures to human volunteers point to one specific component of the mixture--acidic aerosol--as the most likely causal factor for the various demonstrated human health effects.

Lead (Pb) and Nutritional Factors--Effects on Blood Pressure

This case study identifies lead as an independent causal factor for hypertension in adult males among a host of dietary cofactors that were previously known or strongly suspected to affect hypertension. The evidence for the independent role of lead comes primarily from NHANES II, a national population-based study that included a substudy on blood lead, blood pressure, and dietary factors. Supporting evidence for the influence of blood lead on blood pressure comes from a series of recent epidemiological studies of occupationally exposed populations. In retrospect, published data on blood-lead blood-pressure associations in rats could have been used to predict the human association. One reason that the relation was not recognized sooner was its

unusual shape: a plateau of elevation in blood pressure at a relatively low level of blood lead. Most toxicological data are generated at relatively high exposure levels, and effects that occur only at the lower exposure levels are likely to be overlooked.

These two case studies involving multipollutant exposures were not able to demonstrate that pollutant interactions were important. Rather, they indicated the importance of identifying the role of an active agent within the complex mixture. Of the eight case studies in the report, only one was able to demonstrate an interactive effect. That one was a multiplicative effect of cigarette smoking and asbestos exposure on bronchial cancer in occupational groups. On the other hand, there may well have been multiplicative or synergistic effects in other cases: the data bases may have simply been inadequate to demonstrate either their presence or absence.

EVIDENCE FOR MULTIPOLLUTANT INTERACTIONS

The best available evidence for multipollutant interactions comes from controlled laboratory studies, generally involving relatively simple mixtures. The nature of such interactions, and the exposure conditions which produce them, can help us to design field studies with some reasonable prospect of detecting such effects in human populations in the field. Lessons can also be drawn from a review of the results of previous field studies which have sought, and sometimes found, evidence for multipollutant interactions. The following sections review and discuss the results of these laboratory and field studies in terms of the lessons they can provide for the design of future field studies.

Laboratory Studies - Experimental Animals

Most of the studies of air pollutant interactions have used ozone (O_3) in combination with other airborne irritants. The focus on O_3 lies in its own inherent toxicity and its frequent occurrence in ambient air at concentrations which exceed the current NAAQS of 120 parts per billion (ppb)-maximum one hour concentration. O_3 is the only ambient pollutant which produces readily measurable functional decrements and biochemical changes at concentrations frequently encountered in ambient air. For example, single brief O_3 exposures at and below the current NAAQS produce respiratory function decrements in children and adults[2-6], accelerated rates of particle clearance from the lungs of rabbits[7], increased numbers of alveolar macrophages and depressed phagocytosis in rabbit lungs (8), increased mortality in mice challenged with Streptococcus aerosol[9], and elevated creatine kinase activity in blood plasma of rats and mice.[10] One day of exposure at 120 ppb O_3 caused an elevation of the lavagable protein content of rat lungs.[11]

Last et al.[12] have demonstrated synergistic lung damage by O_3 and nitrogen dioxide (NO_2), in association with ammonium sulfate ($(NH_4)_2SO_4$) and H_2SO_4. In rats exposed for 3 days at 0.64 ppm O_3 and 5 mg/m^3 $(NH_4)_2SO_4$, lung macrophages and monocytes were increased 2 to 3x, fibroblasts 2x and collagen synthesis rates 2.5x as compared to rats exposed to O_3 alone. In terms of the frequency of pulmonary lesions of the proximal acinus, there were virtually none in rats exposed to aerosol alone, and the same frequency in rats exposed to aerosol plus O_3 and O_3 alone. However, the lesions in the aerosol plus O_3 group were 50-100% larger than those in the O_3 group. The hypothesis offered

to account for the synergism was that the lifetime of free radicals arising from the oxidant exposure is increased by the local pH changes caused by the acidic aerosol (12). Last and co-workers have demonstrated synergism for O_3 at 0.20 ppm in the presence of an acidic aerosol.[13] In the latter study, synergism was demonstrated between O_3 and sodium chloride (NaCl) or sodium sulfate (Na_2SO_4). On the other hand, there was synergism between NO_2 and NaCl, which was attributed to the formation of nitrosyl chloride.[14] A dose-dependent acidic aerosol enhancement of focal lung lesions in the rat caused by O_3 and NO_2 has also been reported by Kleinman, et al.[15]

Amdur, et al.[16] have demonstrated pollutant interactions for mixtures of 1 ppm SO_2 and 5 mg/m^3 zinc oxide (ZnO) as an ultrafine condensation aerosol when they were mixed together at high temperature in a humid environment under conditions that led to the formation of a surface coating of H_2SO_4 on the ZnO. Three hours of exposure of guinea pigs to this mixture produced significant decrements of lung diffusing capacity (DL_{CO}). At 1 hr after exposure, there was an increase in lung permeability. At 12 hr after exposure, there was distention of perivascular and peribronchial connective tissues, and an increase in lung weight. The alveolar interstitium also appeared distended. At 72 hr after exposure, total lung capacity (TLC), vital capacity (VC) and functional residual capacity (FRC) had returned to baseline levels, but DL_{CO} was still significantly depressed. None of these effects occurred with SO_2 or ZnO alone, or with the mixture in the absence of heat and humidity. Based upon prior experience with pure SO_2 and pure H_2SO_4 exposures in the guinea pig model, Amdur, et al. concluded that, because of its persistence, the humid furnace effluent effect was an acid aerosol effect.

In follow-up studies using repetitive exposures to mixtures containing 1 ppm SO_2 plus 1 mg/m^3 ZnO, TLC, VC, and DL_{CO} were significantly decreased on the 4th day during a 5-day, 3 hr/day exposure regime. When guinea pigs were exposed (1 mg/m^3 ZnO, 1 ppm SO_2, 3 hr/day) for 5 days, rested over the weekend, and then reexposed, the various lung function parameters that were lowered after 5 days of exposure recovered during the weekend rest. However, the next exposure dropped them back to the same level as before the weekend rest period, showing that low level exposure could sensitize the airway to the next assault.[17]

Ehrlich, et al.[18] studied the effects of short-term inhalation of NO_2 and O_3 mixtures on the resistance of mice to streptococcal pneumonia. They investigated the effects of single and multiple daily 3 hr exposures for concentrations of NO_2 ranging from 1.5 to 5.0 ppm, and O_3 ranging from 0.05 to 0.5 ppm. The effects of single exposures were additive. The ability to clear inhaled bacteria from the lungs was diminished in mice exposed to the NO_2-O_3 mixtures for 3 hrs. This impairment was manifested by the increased frequency of isolation of Streptococcus from the lungs for up to 6 days after the respiratory challenge. Excess mortalities observed after 20 daily 3 hr exposures suggested that a synergistic effect might be present upon repeated inhalation of pollutant mixtures, that made them more effective in reducing resistance to respiratory infection.

Sherwood, et al.[19] exposed mice to 1 ppm NO_2, 290 $\mu g/m^3$ $FeSO_4$, and their combination prior to infection with S. aureus or group C streptococci. Exposure to $FeSO_4$ or NO_2 for 48 hr, or to both for 24 or 48 hr, resulted in significant decreases in inactivation of inhaled streptococci. Mortality

occurred earlier, without an increase in deaths.

Aranyi, et al.[20] extended the mouse infectivity model to subchronic exposures to mixtures of O_3, SO_2 and $(NH_4)_2SO_4$. Mice exposed 5 hr/day, 5 day/wk up to 103 days, to 0.1 ppm O_3 or to a mixture of O_3, 5 ppm SO_2, and 1.04 mg/m^3 $(NH_4)_2SO_4$ showed significantly greater susceptibility to group C streptococcal aerosol infection relative to filtered air controls. Pulmonary bactericidal activity by alveolar macrophages was significantly enhanced in the lungs of mice exposed to the mixture relative to those inhaling filtered air or O_3 alone. The total number and distribution of the free cells lavaged from the lungs, as well as cellular ATP levels, did not change due to the pollutant exposures.

Schlesinger and Gearhart[21] examined the effects of combined exposures to NO_2 and H_2SO_4 upon the clearance of insoluble tracer particles from the respiratory region of the lungs. Rabbits were exposed for 2 hr/day for 14 days to either 0.3 ppm NO_2, 1 ppm NO_2, or 500 µg/m^3 of submicrometer sized H_2SO_4 alone, or to mixtures of the low and high NO_2 concentrations with acid. Inhaled singly, both concentrations of NO_2 accelerated clearance while H_2SO_4 retarded it, compared to control. Exposure to the combination of 0.3 ppm NO_2 plus H_2SO_4 resulted in a response which was not different from that due to the acid alone. However, exposure to 1 ppm NO_2 plus H_2SO_4 resulted in a clearance pattern which differed from that of both NO_2 and H_2SO_4, but was more similar to that of the latter.

There have been many attempts to demonstrate multipollutant interactions in controlled human exposure studies, but none of them have been able to produce convincing evidence that interactions are likely to occur under ambient exposure conditions. Hazucha and Bates[22] showed that mixed-gas exposure of 0.37 ppm O_3 and 0.37 ppm SO_2 produced a greater decrease of maximal mid-expiratory flow rate than did the O_3 alone. However, Bell, et al.[23] found less severe acute response to a mixture of 0.37 ppm O_3 and 0.37 ppm SO_2 than had been observed by Hazucha and Bates, and only slightly more severe effects from O_3 + SO_2 than O_3 alone. They suggested that biological adaptation of Los Angeles residents to chronic pollutant exposure was a possible explanation. An explanation for the enhanced response to O_3 + SO_2 was the formation of respirable aerosols containing sulfur compounds such as H_2SO_4. Bell, et al.[23] found that the mixture of 0.37 ppm O_3 and 0.37 ppm SO_2 caused a steady formation of some 100,000-250,000 condensation nuclei per cm^3 (0.02-0.05 µm in diameter) in the exposure chamber, and the fine particles containing sulfur were equivalent to 0.5 to 1.5 µg/m^3 of sulfur as $SO_4^=$. On the other hand, a retrospective study of the aerosol composition used for the original O_3 + SO_2 study of Hazucha and Bates[22] showed 230 µg/m^3 of respirable sulfur aerosol expressed as $SO_4^=$ in the mixture of 0.37 ppm O_3 + 0.37 ppm SO_2.

Stacey, et al.[24] reported that 0.4 ppm O_3 alone produced an increase in specific airway resistance of 27% after 4 hrs of exposure, and mixtures of O_3 with particulate matter produced somewhat larger effects (+ 41.7% with 0.4 ppm O_3 + 0.10 mg/m^3 H_2SO_4, and + 28.5% with 0.4 ppm O_3 + 0.133 mg/m^3 $(NH_4)_2SO_4$).

Kagawa[25] exposed healthy adult volunteers at rest and while exercising to O_3 at 0.15, 0.30 and 0.45 ppm, to SO_2 and NO_2 at 0.3 ppm, and to H_2SO_4 at 0.2 and 0.4 mg/m^3. In the mixed gas exposures, he found that the concentration of O_3 seemed to play an important role in the formation of $SO_4^=$ ion. A

significantly greater decrease of specific airway conductance (Gaw/Vtg) was observed during the exposure to the mixture of 0.15 ppm O_3 and 0.3 ppm SO_2 in comparison with 0.15 ppm O_3 + 0.15 ppm SO_2 exposure, and the decrease of Gaw/Vtg in the mixture of 0.15 ppm O_3 and 0.3 ppm SO_2 was essentially the same as that produced by exposure to 0.3 ppm O_3 alone. The formation of $SO_4^=$ aerosol and fine particles during these exposures may have substantially contributed to the observed synergism in the mixture of O_3 and SO_2. However, the hypothesis that H_2SO_4 aerosol substantially enhances the irritancy of O_3 and SO_2 mixtures was not confirmed in the subjects exposed to the mixture of 0.15 ppm O_3 + 0.2 mg/m^3 H_2SO_4, which was almost the same concentration observed in the mixture of 0.15 ppm O_3 and 0.3 ppm SO_2. The difference between the decrease of Gaw/Vtg after exposure to 0.15 ppm O_3 + 0.3 ppm SO_2 or 0.15 ppm O_3 was significantly ($p < 0.05$) greater than the difference between the decrease after exposure to 0.15 ppm O_3 + 0.2 mg/m^3 H_2SO_4 and that after exposure to 0.15 ppm O_3. This discrepancy might have resulted from the differences of particle size; the diameter of particles formed in the mixture of O_3 and SO_2 was less than 0.03 μm, while that of H_2SO_4 aerosol was 0.7 to 1.1 μm.

Kleinman, et al.[26] exposed human volunteers for 2 hours with intermittent exercise to mixtures of 0.37 ppm O_3, 0.37 ppm SO_2 and a 0.5 μm MMAD sulfate aerosol estimated to contain 115 μg/m^3 of NH_4HSO_4 and 7 μg/m^3 H_2SO_4. The exposure produced a mean decrement in forced expiratory volume in one second (FEV_1) of 3.7%, which was greater than the 2.8% expected for O_3 alone under similar exposure conditions.

The hypothesis that acidic droplet aerosols accounts for the enhanced responses seen by Hazucha and Bates[22] and Kagawa[25] is supported by the results of studies by Amdur, et al.[27] and McJilton, et al.[28] in guinea pigs, and by Koenig, et al.[29,30] on human volunteers. In these studies, exposures to mixtures of SO_2 and NaCl aerosol at high humidity produced a synergistic response in terms of respiratory function parameters. The effect was attributed to SO_2 uptake by droplet aerosols which deposited in small airways. In the later study of Koenig, et al.[30] nine adolescent subjects with extrinsic asthma was exposed for 60 min to 1 mg/m^3 of NaCl, either alone or in combination with 0.5 or 1 ppm SO_2. There were no changes in FEV_1 or flow rate at 50% of vital capacity (V_{50}) after 30 minutes of exposure at rest. However, following 10 minutes of further exposure with moderate exercise, the mean decrements in FEV_1 and V_{50} were 4 and 14% for NaCl alone, 15 and 30% for NaCl + 0.5 ppm SO_2, and 23 and 51% for NaCl + 1 ppm SO_2.

The hypothesis that acidic droplet aerosols enhance respiratory function responses to SO_2 is also supported by the lack of enhancement reported by McJilton, et al. for NaCl-SO_2 mixtures at low humidity, and by Kulle, et al.[31] for mixtures of 1 ppm SO_2 and 0.5 mg/m^3 of activated carbon aerosol. The lack of an enhanced response in the latter study was attributed to the fact that the carbon aerosol sorbed only 10% of the SO_2.

Controlled exposures of human volunteers to complex ambient pollutant mixtures have been performed by Hackney and his colleagues at Rancho Los Amigos Hospital in Downey, CA, using a mobile laboratory. They have exposed volunteers to ambient air, to filtered and purified ambient air, and to mixtures of filtered air and selected pollutants. One of these studies, by Avol, et al.[32] showed that heavily exercising cyclists exposed to ambient air containing 153 ppb O_3 had almost exactly the decrements in FEV_1 and forced vital

capacity (FVC) predicted from their exposures on other test days to mixtures of purified air and O_3. Thus, the other components of the ambient mixture, i.e., 6 ppb SO_2, 40 ppb NO_2, 2.2 ppm carbon monoxide (CO), 295 $\mu g/m^3$ total suspended particulate matter (TSP), 40 $\mu g/m^3$ nitrate (NO_3^-), 13 $\mu g/m^3$ $SO_4^=$, 10 $\mu g/m^3$ ammonium (NH_4^+), etc., had no significant enhancing effect on the O_3 response.

The results of another study performed in the Rancho mobile laboratory suggest that other pollutants may exacerbate the response to O_3. Avol, et al.[33] found that adolescents exposed for 1 hr to ambient air containing 150 ppb O_3 while exercising continuously at 32 L/min had FVC and FEV_1 decrements averaging 108 and 120 mL as compared to their sham exposure to purified air. By comparison, McDonnell, et al.[4] found that 8-11 yr old Chapel Hill, NC children exercising intermittently (3-20 min periods over 2 hrs) at 39 L/min while exposed to O_3 at 120 ppb had FVC and FEV_1 decrements of 40 and 56 mL.

The effective exposures in the two studies were reasonably similar. Since the Chapel Hill children had a greater activity level than the Los Angeles group and were smaller, they should have had greater rather than lesser effects due to the greater relative level of activity. These considerations suggest that either other constituents in the ambient pollutant mixture potentiate the O_3 response, or that children living in Southern California are more responsive to O_3 than children living in North Carolina. The latter hypothesis seems unlikely, since it has been shown that adults living in Southern California are less responsive to O_3 exposures in chambers than are residents of Eastern Canada.[23]

Field Studies

Inferences about possible causal factors have been drawn on the basis of results obtained in many field studies. Confidence in the validity of such inferences depends upon both biological plausibility of the association, and the probability level established by the statistical analyses. Factors which limit the ability of field studies to establish firm causal relationships include: 1) reliance on crude exposure metrics such as TSP; 2) the lack of knowledge about appropriate averaging times for exposure; 3) the unknown relationships between measured ambient concentrations and personal exposures; and 4) the influence of other, often unmeasured, factors such as other pollutants, exposure to mainstream and sidestream cigarette smoke, personal activity levels, diet, etc.

Lebowitz, et al.[5] found that both O_3 and TSP were significantly negatively correlated with peak flow in children and young adults in Tucson, AZ, and had an interactive effect for O_3 in the range 38-120 ppb and TSP in the range 50-125 $\mu g/m^3$.

Bates and Sizto[34] found that hospital admissions for respiratory diseases in summer months from 1974-1982 in Southern Ontario were significant associated with SO_2 lagged 48 hr (L48), with O_3 lagged 24 and 48 hr (L24 and L48), with NO_2 (L48), with $SO_4^=$ (L24 and L48) and with temperature (L24 and L48), while admissions for nonrespiratory disease had no associations with pollutant variables. A multiple regression analysis indicated that $SO_4^=$ (L24) accounted for 3.5% of the variance in respiratory admissions, and that with the addition of $SO_4^=$ on the same day and temperature (L48) 4.4% of the variance

was accounted for. The $SO_4^=$ is most likely a surrogate for acidic sulfate aerosol since ammonium sulfate, the form of sulfate generally present in the highest concentrations, is much less biologically active than the gaseous irritants not selected in the regression analysis.

Ware, et al.[35] studied the effects of ambient sulfur oxides and suspended particles on the respiratory health of 10,106 preadolescent children in six eastern and midwestern U.S. cities. They found that the frequency of cough was significantly associated with the average of 24 hr mean concentrations of SO_2, $SO_4^=$ and TSP. Rates of bronchitis and lower respiratory illness were significantly associated with $SO_4^=$ and TSP, but not with SO_2. There were no significant associations between the pollutant indices and indices of respiratory function.

Ozkaynak and Thurston[36] analyzed 1980 U.S. vital statistics and ambient data bases for $SO_4^=$, fine particles (FP), inhalable particles (IP) and TSP. Of the independent mortality predictors considered in their multiple regression analyses, only $SO_4^=$ and FP were consistently and significantly associated with the reported population specific mortality rates. Furthermore, based on the application of FP source apportionment, particles derived from the iron and steel industry and from coal combustion were found to be more significant contributors to human mortality than soil-derived particles.

The results of a number of other population studies have been examined for the role of specific pollutants within the ambient mixture. Dockery, et al.[37] and Dassen, et al.[38] documented persistent decrements in respiratory function in school children following pollution episodes in which both SO_2 and TSP were elevated for several days. However, they were not able to show any closer association with one pollutant index or the other. By contrast, Lippmann and colleagues found that O_3 was the only pollutant variable that was significantly associated with transient decrements in respiratory function in children engaged in outdoor recreational programs at summer camps.[2-3,6] On the other hand, following a four day summer haze episode which produced a persistent baseline shift in the children's peak flow rates, the association for this effect was equally strong for aerosol acidity as for O_3.[39]

Some of the laboratory studies clearly demonstrate that multipollutant interactions among ubiquitous ambient air pollutants can occur following exposures at realistic levels. On the other hand, most of the population based studies which have demonstrated associations between pollutant exposures and health effects have either implicated only one pollutant or reported that the relative roles of two or more pollutants could not be separated.

STUDY OPPORTUNITIES

While field studies of multipollutant interactions have been largely unsuccessful in the past, they are clearly feasible. The following are some critical factors affecting the prospects for success in such studies. If given sufficient consideration in the study design and execution, prospects for detecting and quantifying pollutant interactions in human population studies could be greatly enhanced.

Appropriate Metrics of Exposure

Far too little attention has been given in the past to the appropriate metrics of exposure in studies of exposure-response. In terms of ubiquitous air pollutants, there has been inadequate attention to averaging time for continuously measured variables such as O_3, SO_2 and NO_2. The effects of O_3 are most likely due to cumulative exposures over multiple hours[7,40], while the only demonstrated effects of SO_2 on respiratory function have an averaging time of considerably less than one hour.[41] One of the pollutant variables most likely to affect measurable responses, i.e., acidic aerosols has seldom been measured at all.[42]

Appropriate Metrics of Response

Much more attention has been given to metrics of response than metrics of exposure. However, it would not be entirely unfair to conclude that much more could be done. The value of standardized questionnaires for respiratory symptoms has been clearly demonstrated in both laboratory and field studies of pollutant health effects. Likewise, the use of standardized protocols for performing respiratory function tests has helped to generate more data of high quality which can be readily interpreted and compared between studies.

On the other hand, there has been too little attention in study design to the question of whether the standardized response metrics are the most appropriate or sensitive ones for the hypothesis being addressed. Furthermore, too little attention has been paid to the temporal interrelationships between exposure and response. Studies of the chronic effects of pollutant exposure on respiratory function may be confounded by the transient changes in the same functions associated with a recent peak exposure. Conversely, studies of transient responses to peak exposures can be confounded by alterations in sensitivity caused by prior chronic exposure.

Emphasis in respiratory function studies is usually given to FVC and FEV_1 because they can be made with more precision than other indices. On the other hand, O_3 generally produces significant changes in peak flow rate before it produces significant changes in FVC or FEV_1.[2-3,6] While peak flow rate is not usually a reported index from a spirometric test, it can be. It is more difficult to introduce nonspirometric indices in field studies. It may, however, be essential to do so if effects, which are being produced by pollutant exposures, are to be detected. Effects of pollutant exposures of interest can be detected with aerosol probe techniques[43], and measurements of particle clearance function[44] for exposures which do not produce measurable changes in spirometric indices.

Appropriate Study Populations

In selecting a population for study of multipollutant interactions there are a number of special considerations which go well beyond the normal criteria for population selection. Of course, due consideration must still be paid to the selection of exposed and control populations for variables such as age, sex, health status, predisposing factors, etc. The additional issues of primary importance relate to the nature of their exposures to the pollutants of interest.

One key question is the likelihood that they have sufficient exposure to elicit a measurable reponse based upon knowledge gained from laboratory studies and prior field studies. If so, are the necessary measurements of both relevant exposure and response feasible under field conditions? A second key question, relating especially to multipollutant interaction, is whether the exposures to the pollutants of interest are highly collinear. Some examples from recent field studies illustrate the problems and opportunities. Table I, from a study of camp children in Ontario[45], shows a high degree of collinearity among the environmental variables of prime interest. On the other hand, Table II, from a study of camp children in New Jersey[6], shows a much lower degree of collinearity. Clearly, separation of the roles of the different exposure variables is much easier for the latter case than for the former.

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TABLE I: Correlation Coefficients-Aerometric Variables in Canadian Childrens Camp Study-1983

	$SO_4^=$	O_3	TEMP
FP	0.92	0.86	0.81
$SO_4^=$		0.78	0.67
O_3			0.77

TABLE II: Correlation Coefficients-Aerometric Variables in New Jersey Childrens Camp Study-1984

	H^+	O_3	TEMP
IP	0.44	-0.03	0.19
H^+	-	0.13	0.30
O_3	-	-	0.37